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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,158	10/25/2001	Masayoshi Nanba	46342/56603	8650
21874	7590	10/03/2003	EXAMINER	
EDWARDS & ANGELL, LLP P.O. BOX 9169 BOSTON, MA 02209			SWOPE, SHERIDAN	
			ART UNIT	PAPER NUMBER

1652

DATE MAILED: 10/03/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/009,158	Applicant(s) NANBA ET AL.	
	Examiner Sheridan L. Swope	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) 5-14 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-4 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>18</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response, on June 16 and July 17, 2003, Paper Nos. 17 and 19, to the first Office Action on the Merits of this case is acknowledged. It is acknowledged that applicants have amended Claims 1-4. Claims 1-4 are hereby reconsidered.

Claim Rejections - 35 USC § 112-First Paragraph

Rejection of Claims 1 and 2 under 35 U.S.C. 112, first paragraph, for the reasons described in the prior action, is maintained.

Applicants provide the following arguments in support of their request for withdrawal of said rejection. That, cells to be used in the instant invention should not be limited, for example, to HepG2 cells because the present invention makes it possible to evaluate total metabolism and oxidative metabolism by stable expression of cytochrome P450. That, examples of other liver-derived cells, such as HLE, PLC/PLF/5, HuH-6, HuH7, Hep3B, and the like are known in the art and may be useful in the practice of the present invention. These arguments are not found to be persuasive for the following reasons.

It is acknowledged that cells, other than HepG2, may be useful for the instant invention. However, Miyazaki et al teach that HepG2 cells are “chromosomally abnormal, with a modal number of 55, and contain distinctive rearrangement of chromosome 1” (in IDS, pg 203, col 2, lines 1-2). Said teachings indicate that HepG2 cells are not the same as every other hepatocarcinoma cell line; thus, the utility of HepG2 cells for analysis of heterologous P450 enzymes may not be shared by all other hepatocarcinoma cell lines. The specification and knowledge in the art fails to provide sufficient guidance for how a person of ordinary skill in the art would select those cell lines that are useful without screening all lines derived from any

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human hepatocarcinoma cell. Such screening represents undue experimentation. Applicant's disclosure in their rebuttal that, the HLE, PLC/PLF/5, HuH-6, HuH7, and Hep3B cell lines are useful in the instant invention can not be considered as guidance, as said cell lines are not disclosed in the specification. Therefore, rejection of Claims 1 and 2 under 35 U.S.C. 112, first paragraph, for the reasons described in the prior action, is maintained.

Claim Rejections - 35 USC § 103

Rejection of Claims 1-3 under 35 U.S.C. 103(a) as being unpatentable over Dai et al, 1993 in view of GenBank Acc# J04449, 1994 and further in view of Waxman et al, 1991, for the reasons described in the prior action, is maintained.

Applicants provide the following arguments in support of their request for withdrawal of said rejection. That, a gene transfer system using vaccinia virus is usable for transient expression, which is totally different from a stable or constitutive expression system. That, the possibility of stable expression of CYP3A4 cannot be suggested by transient expression of CYP3A4 using vaccinia virus. That, the choice of a plasmid-mediated method has a sound technical basis and is not merely a matter of convenience. That, the plasmid-mediated method of Dai et al is more difficult to utilize than the method using a vaccinia virus. That, there is no motivation in Waxman et al or in Dai et al to combine these two reference to establish the stable expression of CYP3A4 using HepG2. These arguments are not found to be persuasive for the following reasons.

It is acknowledged that expression of heterologous genes with viruses is different from expression with plasmids. A person of ordinary skill in the art would know the advantages and disadvantages of both approaches. Said person of skill, upon learning the teachings of Waxman

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et al, would known the advantages of using plasmids, instead of vaccinia virus, to stably express CYP3A4 in HepG2 cells. As applicants point out, the use of stable expression systems provides the benefits of observing metabolic activities in living cells; said benefits would be of common knowledge to a person of skill in the art. The Examiner does not agree that the plasmid-mediated method of Dai et al is more difficult to utilize than the method using a vaccinia virus.

Preparation and storage of viruses is much more difficult than preparation and storage of plasmids. Using viruses, new cells must be reinfected for each experiment; thus, both virus and infected cells must be prepared for each experiment. In contrast, using plasmids, cells are transfected only once and readily available for experimentation. This ease of propagation and the obvious experimental benefits of stable transfection with plasmids, provide clear motivation to use the plasmid-mediated methods of Dai et al to stably express CYP3A4 in HepG2.

Appreciation of such motivation would be common knowledge to a person of ordinary skill in the art. Thus, Rejection of Claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Dai et al, 1993 in view of GenBank Acc# J04449, 1994 and further in view of Waxman et al, 1991 is maintained.

Allowable Subject Matter

Claim 4 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

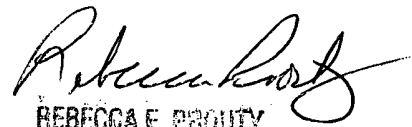
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 703-305-1696.

The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan L. Swope, Ph.D.


REBECCA E. PROUTY
PRIMARY EXAMINER
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